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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/975,723	10/11/2001	Gary Nackman	601-1-101N	8417

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EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/975,723	NACKMAN ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *16-22 and 28-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 23-27* is/are rejected.

7)☒ Claim(s) *2-15 and 24-27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *21 October 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CLAIMS STATUS

1. Claims 1-34 are pending.

Restriction/Election

2. Applicants' election with traverse of Group I, Claims 1-15 and 23-27 filed 28 July, 2004 in reply to restriction requirements in Office Action dated 21 June 2004 is acknowledged and entered. The traversal is on the ground (s) that a search for the invention encompassing Claims in Group I would automatically result in a search for the claims encompassed in invention of Group IV. Applicants further argue that a search for the aforementioned groups would not place an additional burden on the examiner. Applicants suggest that Examiner should examine said two groups, if the search and examination will not cause serious burden, "even though the claims are drawn to independent inventions" because according to MPEP §808.02 restriction is not required unless one of the following reasons appear:

i. separate classification,
ii. separate status in the art, or
iii. different field of Search.

Applicants' arguments regarding the restriction requirements in the above cited response to Office Action dated 21 June 2004 have been carefully and fully considered but are not found persuasive because of the reasons of record at page 4 of the Office Action dated 21 June 2004. As pointed out in said Office Action, for purposes of the initial restriction requirement, Examiner has *prima facie* shown by appropriate explanation separate classification (see Classification and sub-classification assigned to different invention groups), separate status in the art, and a different field of search as defined in MPEP §808.02 that the inventions in Groups I and IV are distinct. Thus, t he search for each one of inventions in Groups I and IV is not coextensive particularly with regard to the literature search. Further, a reference that would anticipate the invention of one group would not necessarily anticipate, or even make obvious another group. Finally, the consideration for patentability is different in each case. Thus, it would be an undue burden to examine inventions encompassed in Groups I and IV in one application.

Accordingly, Claims 16-22 and 28-34 are withdrawn from further consideration as being directed to a non-elected invention. See 37 CFR §1.142(b) and MPEP § 821.03. Examiner suggests that the non-elected claims cited above be canceled in response to this Office action to expedite prosecution.

Claims 1-15 and 23-27 are examined on merits.

Information Disclosure Statement

3. Applicants' Information Disclosure (i.e., IDS) filed 21 October 2002 has been made of record and considered.

Priority

4. Applicants' claim for domestic priority under 35 U.S.C. §120 is acknowledged.

Objection To Specification

5. The specification is objected to because certain terms (e.g., complete medium at Page 15, Line 4) are not defined in the specification.

Claims Objection

6. Claims 2-15 and 24-27 are objected to for following reasons:

- Claims 2-7, 10-15 and 24-27 are objected to because at Line one of the each of the cited Claims the first appearance of letter "A" is inappropriate. Examiner suggests that first appearance of letter "A" at Line one of each of the cited Claims should be replaced with the word --The-- to clarify the dependence for each of the referenced claims. Applicants are cautioned to ensure that no new matter is added while this replacement of letter "A" with the word "The" is made.

- Claims 7-9, 11-15. 25 and 27 are objected to because at Line one of each one of the cited Claims, before the word "wherein" a --, -- should be inserted. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

8. Claims 24 and 27 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

- The recitation "cadherin in native vascular endothelial cells" in Claim 24 renders that claim vague, unclear and indefinite, because the metes and bounds for the phrase "native vascular endothelial cells" are not defined in either in the specification or the claim language and one skilled in the art would not be reasonably apprised of the scope of the invention to distinguish between native and non-native vascular endothelial cells because the metes and bounds for the term "native" are not clear. Applicants should clearly define metes and bounds for the phrase, "cadherin in native vascular endothelial cells".

- The recitation "functional molecules" in Claim 27 renders that claim vague, unclear and indefinite, because the metes and bounds for the phrase "functional molecules" are not defined in either in the specification or the claim language and one skilled in the art would not be reasonably apprised of the scope of the invention to distinguish between functional and non-functional molecules because the metes and bounds for the term "functional molecules" are not clear. Applicants should clearly define the metes and bounds for the phrase, "functional molecules".

Claim Rejections - 35 U.S.C. § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> ***(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.***

10. Claims 1-2, 4-6, 10 and 12-15 are rejected under 35 U.S.C. §102(b) as anticipated by Schnittler et al., American J. Physiol., 1997, Volume 273, Pages H2396-H2405).

Claims recite a method to populate a solid surface via enhancing cell to cell cohesion, wherein said cells are human vascular endothelial cells and said enhancement is brought by reducing cadherin dissociation from cytoskeleton, or increasing amount of cadherin per cell. Said cadherin is an eukaryotic/ mammalian cadherin polypeptide, specifically a human cadherin polypeptide selected among: E- N-, P- or VE-cadherin polypeptide.

Schnittler et al. teach a method to populate human umbilical venous endothelial cells on glass cover slips and enhance cell to cell cohesion for said cells via enhancing concentration of cadherin, wherein said cadherin is VE-cadherin through recalcification (Abstract, Lines 11-30; Page H2396, Column 1, Lines 57-60 and Page H2397, Column 1, Lines 21-30) because at lowering calcium concentrations,

cadherin and β-catenin disappear at cellular junction, i.e., molecules associated with adherens junction between the cells disappear(Abstract, Lines 11-30, Page H2400, Column 1, Line 17 to Column 2, Line 20). Schnittler et al. demonstrate further proof of cadherin enhancement in association with cell- to cell cohesion because they teach that during the production of a confluent monolayer comprised of endothelial cells, VE-cadherin was the first to be observed at the intercellular junction. Thus, Schnittler et al. clearly teach populating a solid surface via enhancing cell to cell cohesion through reducing dissociation from cytoskeleton/ enhancing concentration of cadherin, wherein said cadherin is a mammalian/human VE-cadherin polypeptide.

Therefore, the reference is deemed to anticipate the cited claims.

11. Claims 1-7, 9-10, 12-15 and 23-27 are rejected under 35 U.S.C. §102(b) as anticipated by Hordijk et al. (J. Cell Sci, 1999, Volume 112, pages 1915-1923) with evidence provided by Stedman's Medical Dictionary (1995. Williams and Wilkins, Baltimore).

Claims recite a method to populate a solid surface via enhancing cell to cell cohesion, wherein said cells are human vascular endothelial cells and said enhancement is brought by reducing cadherin dissociation from cytoskeleton, or increasing amount of cadherin per cell. Said reduction in dissociation from cytoskeleton is brought by reducing phosphorylation of a molecule associated with adherens junction between said endothelial cells or increasing the functional molecules bridging the cadherins to cytoskeleton. Said cadherin is an eukaryotic/ mammalian cadherin polypeptide, specifically a human cadherin polypeptide selected among: E- N-, P- or VE-cadherin polypeptides.

Hordijk et al. teach a method to populate HUVEC (i.e., human umbilical venous endothelial cells) on glass cover slips or polycarbonate membranes (Page 1916, Column 1, Lines 47-65) and enhance cell to cell cohesion (i.e., adhesion) for said cells via localizing VE-cadherin because upon inhibiting VE-cadherin, cell to cell adhesion was lost (Summary, Lines 1–11; Page 1915, Column 1, Lines 311-36, Page 1919, Column 2, Lines 40-47). With localization of VE-cadherin, F-actin, β-catenin and plakoglobin (i.e., γ-catenin), i.e., molecules associated with adherens junction between the cells were also observed (Page 1916, Column 1, Lines 20-35; Page 1915, Column 1, Lines 30-45). Thus, Hordijk et al. teach that cadherin-catenin complexes are involved in cellular cohesion and that enhancement of VE-cadherin localization promotes VE- cadherin mediated cell to cell cohesion (Page 1918, Column 2, Lines 7-23). Hordjik et al. further teach that enhanced VE-cadherin mediated cell to cell adhesion also manifest increased levels of c-AMP (Page 1919, Column 1, Lines 36-39). Thus, inherently, Hordijk et al. teach a method to populate a solid surface with cells via enhancement in cell to cell cohesion through reducing cadherin dissociation from cytoskeleton via reducing phosphorylation of a molecule associated with

adherens junction because with localization of VE-cadherin, F-actin was also observed and during formation of F-actin from G-actin bound ATP molecule is converted to ADP (See Stedmans Medical dictionary, Page 20, Column 1, Lines 54-59).

Therefore, the reference is deemed to anticipate the cited claims.

In this rejection under 35 U.S.C. §102(b) Stedman's Medical Dictionary (1995. Williams and Wilkins, Baltimore) is cited to merely support that the formation of F-actin is associated with reducing phosphorylation of an adherens junction molecule, and said reference is not cited as a prior art reference.

12. Claims 1,5 and 10-11 are rejected under 35 U.S.C. §102(b) as anticipated by Navarro et al. (Journal of Biological Chemistry, 1995,Volume 270, Pages 30965-30972).

Claims recite a method to populate a solid surface via enhancing cell to cell cohesion, wherein said cells are human vascular endothelial cells and said enhancement is brought by increasing amount of cadherin per cell. Said cadherin is increased by increasing expressible cadherin genes in the endothelial cells.

Navarro et al. teach a method to populate human umbilical cord venous endothelial cells on 24 well plates (Page 30966, Column 2, Line 70 to Page 30967, Column 1, Line10 under Figure 1) and promote cell aggregation via gene expression for VE-cadherin and in contrast to wild-type (i.e., genetically un-engineered) VE-cadherin, genetically modified VE-cadherin was more efficiently concentrated at cell to cell contacts (Page 30971, Column 1, Lines 2-10; Column 2, Lines 2-8).

Therefore, the reference is deemed to anticipate the cited claims.

Claim Rejections - 35 U.S.C. § 103

13. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of

each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § *102*(f) or (g) prior art under 35 U.S.C.§ 103(a).

15. Claims 1-15 and 23-27 are rejected under 35 U.S.C. § 103 (a) as obvious over Schnittler et al., American J. Physiol., 1997, Volume 273, Pages H2396-H2405) in view of Hordijk et al. (J. Cell Sci, 1999, Volume 112, pages 1915-1923) with evidence provided by Stedman's Medical Dictionary (1995. Williams and Wilkins, Baltimore) and Navarro et al. (Journal of Biological Chemistry, 1995,Volume 270, Pages 30965-30972).

Claims recite a method to populate a solid surface via enhancing cell to cell cohesion, wherein said cells are human vascular endothelial cells and said enhancement is brought by reducing cadherin dissociation from cytoskeleton, or increasing amount of cadherin per cell. Said reduction in dissociation from cytoskeleton is brought by reducing phosphorylation of a molecule associated with adherens junction between said endothelial cells or increasing the functional molecules bridging the cadherins to cytoskeleton. Said cadherin is an eukaryotic/ mammalian cadherin polypeptide, specifically a human cadherin polypeptide selected among: E- N-, P- or VE-cadherin polypeptides. Said increase in amount of cadherin per cell is brought by increasing expressible cadherin genes in the endothelial cells.

Teachings from Schnittler et al., Hordijk et al. with evidence provided by Stedman's Medical Dictionary and Navarro et al. have already been discussed *supra*.

One having ordinary skill in the art at the time of the claimed invention would have been motivated to modify/combine the teachings from Schnittler et al. according to teachings from Hordijk et al. with evidence provided by Stedman's Medical Dictionary and Navarro et al. to obtain a method to populate a solid surface with human vascular endothelial cells via enhancing cell to cell cohesion, wherein said enhancement is brought by either reducing cadherin dissociation from cytoskeleton, or increasing amount of cadherin per cell, wherein said cadherin is one of E-,N-, P- or VE-cadherin polypeptide and cadherin dissociation is reduced via reducing phosphorylation of an adheren junction associated molecule or increase in cadherin is brought by increasing expressible cadherin genes in said endothelial cells, because each of the prior art references teach populating a solid surface via enhancing cell to cell cohesion in human umbilical cord venous endothelial cells. Schnittler et al. teach different types of cadherin (e.g., VE-cadherin) and method to enhance cadherin, β-catenin and plakoglobin (i.e., γ-catenin), i.e., molecules associated with adherens junction; Hordijk et al. teach localization of VE-cadherin, F-actin, β-catenin and plakoglobin (i.e., γ-catenin), i.e., molecules associated with adherens junction as well as reduction in phosphorylation of an adheren junction molecule (i.e., F-actin) during the cell to cell cohesion mediated cell growth on a solid surface and Navarro et al. teach a method to populate human

umbilical cord venous endothelial cells via promoting cell aggregation through gene expression for VE-cadherin. Hordijk et al. remedy the deficiency of reducing the cadherin dissociation from cytoskleton via de-phosphorylation of a molecule associated with adherens junction in the teachings from Schnittler et al., while Navarro et al. remedy the deficiency of enhancing the cadherin via gene expression in Schnittler et al's teachings.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify teachings from Schnittler et al. with those from Hordijk et al. with evidence provided by Stedman's Medical Dictionary and Navarro et al. to obtain a method to populate a solid surface with human vascular endothelial cells via enhancing cell to cell cohesion, wherein said enhancement is brought by either reducing cadherin dissociation from cytoskeleton, or increasing amount of cadherin per cell, wherein cadherin is one of E-,N-, P- or VE-cadherin polypeptide. Hordijk et al. remedy the deficiency of reducing the cadherin dissociation from cytoskleton via de-phosphorylation of a molecule associated with adherens junction in the teachings from Schnittler et al., while Navarro et al. remedy the deficiency of enhancing the cadherin via gene expression in Schnittler et al's teachings. Instantly claimed adherens junction associated molecule to be dephosphorylated for reducing cadherin dissociation from cytoskeleton is not the same as that taught in the cited prior arts. However, the adjustment of particular conventional working conditions (e.g., selection of a particular cadherin-catenin-actin cytoskeleton complex component) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter which is well within the purview of the skilled artisan.

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

16. No Claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 8:15 A.M. to 6:45 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743 Monday through Thursday. The fax phone number for the organization where this application or proceeding is assigned is (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Kailash C. Srivastava, Ph.D.
Patent Examiner
Art Unit 1651
(571) 272-0923

October 18, 2004

RALPH GITOMER
PRIMARY EXAMINER
GROUP 1200